REMARKS

Status of the Claims

Claims 1, 3 to 9, 21, 22 and 25 to 27 were pending as shown in the response filed November 25, 2005. Claim 1 has been amended as shown above to replace the recitation "derived from an antibody" with the phrase "antibody or derivative thereof," as described, for example, on page 15, lines 8-12. Claim 1 has also been amended to replace the recitation "selectively recognizes" with "binds to," as described, for example, on page 14, lines 24-27 of the specification. In addition, claims 1, 9 and 26 have been amended as suggested by the Examiner to provide complete recitations for antecedent basis.

Thus, claims 1, 3-9, 21, 22, 25, 26 and 27 are pending as shown above.

35 U.S.C. §103

Claims 1, 3-9, 22-23 and 27 were again rejected under 35 U.S.C. § 103(a) as allegedly anticipated by U.S. Patent No. 5,650,135 to Contag in view of U.S. Patent No. 5,348,867 to Georgiou. (Office Action, pages 3-4).

Contag was cited for disclosing biocompatible entities (*e.g.,* cells, molecules such as antibodies, microorganisms, particles) conjugated to a light emitting moiety. (Office Action, pages 2-4, citing col. 3, lines 11-14; col. 4, lines 18-21 and col. 7, lines 31-39 of Contag). It was also noted that Contag discloses conjugates comprising bacterial cells transformed with sequences encoding a light-generating protein and which cells also express an antibody on their surface to target the cells to a particular antigen when administered to a subject. *Id.* While the Office Action states that Contag does not explicitly disclose expression of the antibodies or antibody fragments on the bacterial surfaces, it was alleged that it would have been obvious to use Georgiou's heterologous scFV antibodies in Contag's biocompatible entities (transformed cells expressing a light generating protein and an antibody). *Id.*

Applicants traverse the rejection and supporting remarks.

The pending claims are drawn to biodetectors which comprise the following 3 elements: (1) a transmembrane fusion protein having an extracellular antibody (or derivative thereof) domain and an intracellular domain which is activated upon binding of a selected substance to

the antibody; (2) a transducer which is activated by the activated intracellular domain of the transmembrane fusion protein; and (3) a transcription activation element that is activated by said active form of the transducer, to give a detectable signal.

Although Contag is the seminal work in the area of non-invasive *in vivo* imaging, the Office has not demonstrated that this reference teaches or suggests biodetectors as claimed. In particular, Contag describes how to administer a conjugate comprising a light-emitting moiety (*e.g.,* a sequence encoding a bioluminescent protein operably linked to an inducible promoter) and a biocompatible entity (*e.g.,* cell comprising the sequence encoding the light-generating protein, antibody) to a mammalian subject and how to image the light emitted from the conjugate through opaque tissue of the live mammal. *See, e.g.,* col. 2, line 62 to col. 3, line 5 of Contag.

However, the conjugates described in Contag are not biodetectors as set forth in the pending claims.

In terms of fusion proteins comprising an extracellular antibody portion (element (a) of claim 1), Contag does not teach a fusion protein in which the extracellular antibody domain activates an intracellular enzymatic domain upon binding of the antibody to a selected substance. Instead, Contag teaches a protein in which the antibody portion is conjugated to a sequence encoding a light-generating protein (see, col. 3, lines 6-10):

> The moiety may be conjugated to the entity by a variety of techniques, including incorporation during synthesis of the entity (e.g. chemical or genetic, such a fusion protein of an antibody fragment and a light-generating protein).

By contrast, the claimed biodetectors, the fusion protein comprises the antibody portion and an enzymatic intracellular portion. In the claimed biodetectors, the antibody portion is never conjugated to the detectable responsive element (*e.g.,* sequence encoding a light-generating protein) as is described in Contag.

Furthermore, with regard to the conjugates described in Contag in which an antibody is used to target a biocompatible entity (*e.g.,* bacterial cells transformed with a light generating protein) to a specific site in the subject (*see, e.g.,* col. 3, lines 35-46 of Contag), Applicants note that the antibody portion of these conjugates is used for targeting, not to trigger a cascade that eventually results in production of a detectable signal, as set forth in the claimed biodetectors. In other words, the Office has not pointed to where Contag teaches or suggests critical elements of

the claimed biodetectors, namely that binding of the antibody portion to its target activates the intracellular domain, which activated intracellular domain then activates a transducer and, which activated transducer causes the responsive element to produce a detectable signal.

In sum, Contag does **not** disclose or suggest a transmembrane fusion protein whose intracellular portion is activated by binding to the extracellular antibody portion; a transducer which is activated by the activated intracellular portion of the fusion protein; and/or a responsive element that is activated by the activated from of the transducer.

Georgiou does not cure the deficiencies of Contag. Indeed, combining Georgiou's disclosure of expressing proteins (including scFV fragments) on the surface of cells with Contag's non-invasive imaging methods cannot result in the claimed biodetectors. This combination would result, at best, in a transformed cell as described in Contag that is targeted to tissues expressing the antigen recognized by the scFV fragments (as described in Georgiou) expressed on the surface of the cell. The scFV fragment would still not trigger expression of the light-generating sequence (via an activated intracellular domain and activated transducer), as claimed.

Thus, the Office has not established that the conjugates described in Contag are biodetectors as set forth in the pending claims or that the combination of Contag and Georgiou can in any way result in biodetectors as claimed. Accordingly, withdrawal of this rejection is respectfully requested.

35 U.S.C. §112, 1st Paragraph (New Matter)

Claims 1, 3-9, 21, 22 and 25-27 were rejected under 35 U.S.C. § 112, 1st paragraph as allegedly containing new matter in light of the amendment to claim 1 reciting "transmembrane fusion protein comprising an extracellular ligand-specific moiety derived from an antibody and an intracellular enzymatic signal transforming domain." (Office Action, page 4).

Applicants respectfully traverse the rejection and supporting remarks.

Applicants direct the Examiner's attention to the following passages where the foregoing recitation in claim 1 is clearly disclosed (*see,* page 11, lines 3-7; page 14, lines 24-27 and page 15, lines 8-12, emphasis added):

In the depicted example, the biodetector is a bacterial cell expressing a transmembrane target specific signal converting element, comprising an extracellular ligand-specific binding moiety, *e.g.,* an antibody, which is coupled to an intracellular signal transforming domain.

Typically, the signal converting element will be a **transmembrane fusion protein composed of an extracellular ligand-binding portion *e.g.,* an antibody and an intracellular enzymatic portion**, which is activated upon binding of the extracellular portion to a selected target.

In specific embodiments, the ligand-binding domain is an antibody or a derivative thereof, including but not limited to polyclonal antibodies, monoclonal antibodies (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab)'2 fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

In view of the foregoing, Applicants respectfully request withdrawal of this rejection.

35 U.S.C. § 112, 2nd Paragraph

Claims 1, 3-9, 21, 22 and 25-27 were rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly indefinite. (Office Action, page 5). In particular, claim 1 was alleged to be indefinite for use of the phrase "derived from an antibody" and for use of the term "selectively recognizes." *Id.* In addition, it was alleged the recitations "said substance" in claim 9; "said fusion protein" in claim 26 and "said intracellular transforming domain" in claim 1 all lacked sufficient antecedent bases. *Id.*

Although Applicants submit that the claims were more than sufficiently clear as previously pending, the rejections have been obviated by the foregoing amendments. Claim 1 has been amended to recite "an antibody or derivative thereof" as set forth, for example, on page 15, lines 8-10 and to indicate that the antibody "binds to" the selected substance as set forth, for example, on page 14, lines 24-27.

Furthermore, claim 1 has been amended to recite "said intracellular enzymatic signal transforming domain; claim 9 has been amended to recite "said selected substance;" and claim 26 has been amended to recite "said transmembrane fusion protein," thereby obviating the concerns regarding antecedent basis. Withdrawal of the rejections is requested.

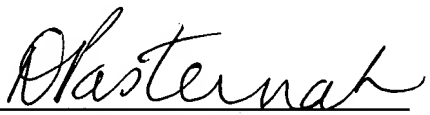
CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

Date: May 4, 2006

By: 

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